Looking but not seeing: recent perspectives on Posterior Cortical Atrophy (PCA)

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Current Directions in Psychological Science

Looking but not seeing: recent perspectives on Posterior Cortical Atrophy (PCA)

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Abstract

Posterior cortical atrophy (PCA) is the canonical 'visual dementia', with affected individuals experiencing a progressive disintegration of their visual world owing to dysfunction and atrophy at the back of the brain. The syndrome, which also affects literacy, numeracy and gesture, is typically caused by Alzheimer's disease (AD), but this atypical form of AD is distinguished from more common amnestic presentations by virtue of relatively preserved episodic memory and insight. Although problems with object and space perception are the most widely reported and investigated symptoms, these higher order perceptual difficulties are often underpinned by an array of changes in more basic visual and oculomotor processes. Here we review recent studies providing insights into these more elementary aspects of vision in PCA, including fixation stability, saccade generation, point localization, excessive crowding, and factors affecting the effective field of vision. It is argued that a more detailed appreciation of these fundamental changes in the early visual system will not only improve the characterization and understanding of this rare clinico-radiological syndrome, but will also guide the design of visual aids and strategies aimed at maintaining everyday abilities in individuals with PCA.

Keywords: Posterior cortical atrophy; Alzheimer's disease; vision; oculomotor; crowding; dyslexia

Posterior cortical atrophy (PCA) is a clinico-radiological syndrome characterized by insidious decline primarily in visuoperceptual and visuospatial processing and dysfunction or atrophy of the posterior cortices (Benson et al., 1988; Mendez et al., 2002; Tang-Wai et al., 2004; see Crutch et al., 2012 for a review). Common presenting symptoms include difficulties with driving, reading, typing and other tasks which involve interpreting, locating, and/or reaching for objects under visual guidance, with additional problems reading, writing, spelling, numeracy and praxis. By contrast, episodic memory and insight are relatively spared. These symptoms are typically associated with hypometabolism and atrophy particularly in parietal, occipital and occipito-temporal cortex (see Figure 1).

The most common pathology in PCA is Alzheimer's disease (AD), with PCA constituting a common form of atypical AD (McKhann et al., 2011; Dubois et al., 2014). A small proportion of cases are due to Lewy body disease and corticobasal degeneration (Hof et al., 1990; Renner et al., 2004). In those PCA patients with Alzheimer's pathology, the distribution of pathological changes differs from that in typical AD, with lower plaque and tangle counts in the medial temporal regions and frontal cortices and relatively higher counts in posterior cortices such as the occipital lobes (Hof et al., 1990; Tang-Wai et al., 2004). However on molecular imaging the focal posterior pattern of cortical involvement is evident with tau-imaging but less clear cut with amyloid imaging where results indicate a more global pattern of amyloid deposition (Ossenkoppele et al., 2015; see Figure 1b). These findings suggest that tau is more closely linked to symptomatology than amyloid. PCA is typically a younger-

onset, sporadic condition (age 50–65 years) (Mendez et al., 2002; Tang-Wai et al., 2004; McMonagle et al., 2006).

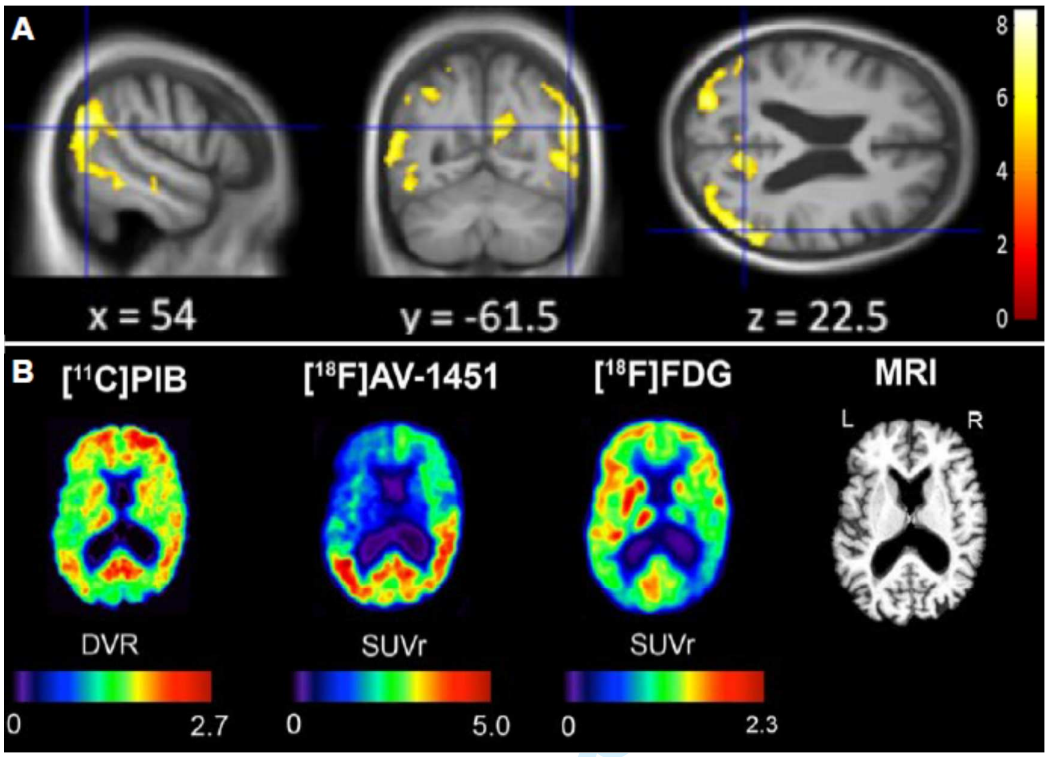


Figure 1. (A) Differences in gray matter volume between individuals with PCA and healthy controls revealed by voxel-based morphometry. Yellow overlay represents T scores in areas of statistically significant lower gray matter volume in PCA (FWE corrected at P<0.05). Images shown in neurological convention (right on right). Crosshairs and co-ordinates (in MNI space) indicate T score global maxima. Adapted from Ryan, Shakespeare et al. (2014). (B) Axial slices of fibrillary amyloid-beta ([11C] PIB: Pittsburgh compound B), regional tau load ([18F]AV-1451), and glucose metabolism ([18F]fluorodeoxyglucose (FDG) positron emission tomography) alongside structural magnetic resonance imaging (MRI) scan in a single patient with PCA. [(11) C]PIB binds throughout association neocortex whilst

[(18) F]AV-1451 is selectively retained in posterior brain regions that were affected clinically and which show reduced [(18) F]FDG uptake. DVR = distribution volume ratio. SUVr = standardized update value ratio. Adapted from Ossenkoppele et al. (2015).

The current paper focuses upon studies directly examining aspects of basic visual and oculomotor function in PCA. Clinical studies have tended to examine high-level object and space perception problems (e.g. the perception of single or multiple whole objects, faces or words, of which patients complain directly) which rely on cognitive processes associated with parietal and occipito-temporal mechanisms downstream in the visual system. By contrast, more basic visual functions (e.g. edge detection, form and motion coherence) which may underpin many such downstream deficits and which are mediated largely by upstream occipital mechanisms, have been largely overlooked. Understanding these basic visual aspects is of interest not just to better characterize the syndrome, but also in order to develop a better understanding of the underpinnings of visual impairments in PCA and develop rehabilitative or compensatory strategies. Furthermore, a sound understanding of the basic visual and oculomotor deficits present in these patients is critical for the design and interpretation of clinical and neuroscientific studies involving individuals with PCA.

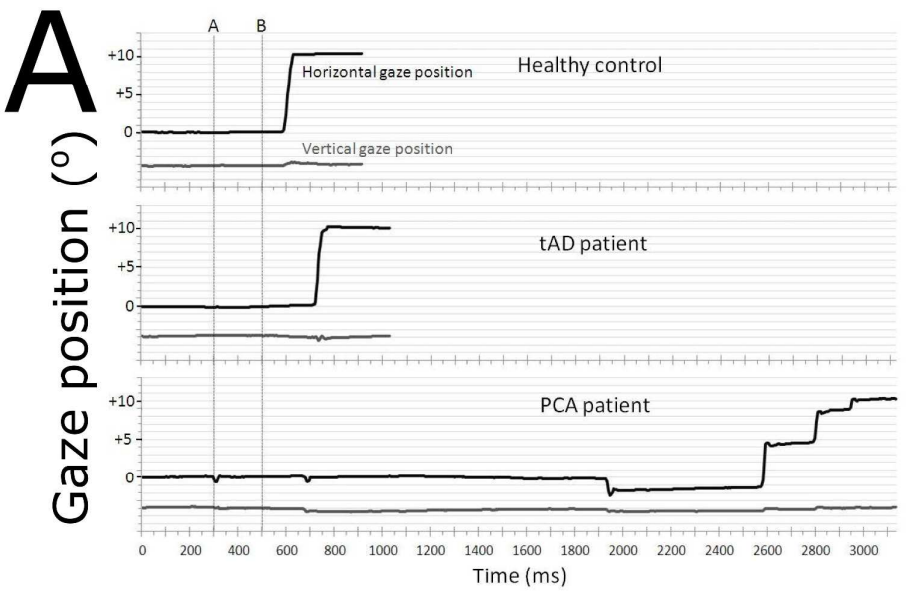
Here we consider the insights provided by recent studies of fixation stability, saccade generation and smooth pursuit aspects of oculomotor function, and point localization, visual crowding, and factors affecting the effective field of vision. We also consider current translational research informed by these

insights including attempts to facilitate reading and room navigation in PCA. The paper concludes with discussion of three avenues for future research illustrating aspects of the syndrome that extend beyond visual deficits, namely visuo-vestibular interactions, motor deficits and representation of concepts related to quantity.

Oculomotor function

A recent systematic evaluation of oculomotor function has shown that eye movement abnormalities are near-ubiquitous in PCA (Shakespeare et al., 2015a). Using tests of fixation, saccade (fixation/target gap and overlap conditions) and smooth pursuit eye movements, eye movement abnormalities were detected in 80% of PCA patients compared to 17% of typical Alzheimer's disease (tAD) and 5% of controls. On fixation stability tasks, PCA patients exhibit micro-saccadic and large saccadic intrusions, which may account for experience of apparent motion or unsteadiness amongst static objects reported by many PCA patients (Crutch et al., 2011). Saccade generation was particularly affected, with PCA patients making significantly shorter saccades especially for distant targets. They also exhibited a significant exacerbation of the normal gap/overlap effect, consistent with 'sticky fixation' (see Figure 2a). PCA patients also showed lower gain in smooth pursuit than controls (see Figure 2b). These oculomotor deficits may reflect weak input from degraded occipito-parietal spatial representations of stimulus location into a superior collicular spatial map for eye movement regulation. In other words, in PCA it may be the identification of oculomotor targets rather than the generation of oculomotor movements which is

particularly problematic. If this hypothesis is correct, precise stimulus localization and spatial attention may play a particularly critical role in determining the adequacy of real world perception in everyday life.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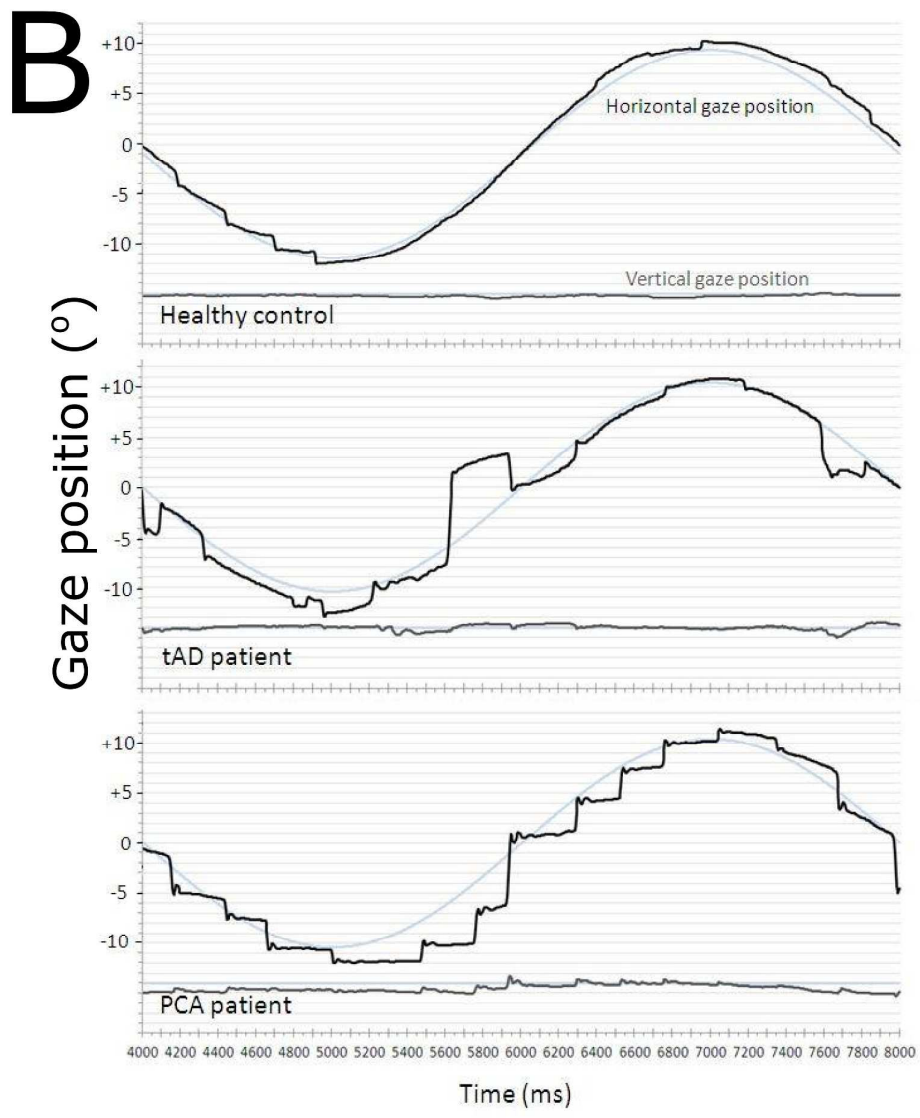
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Figure 2. Abnormalities of fixation and pursuit in PCA (figures adapted from Shakespeare et al., 2015a). (A) Representative traces from the saccade task for a healthy control, a typical AD (tAD) patient and a PCA patient in an 'overlap' trial. The upper plot (grey line) for each participant shows gaze position in the y (vertical) axis, the lower plot (black line) shows gaze position in the x (horizontal) axis. Gridlines show displacement of 1° of visual angle. Positive values of gaze position indicate rightward gaze. A central fixation point was present from the start of the trial until timepoint B (500ms). The target appeared at 10° horizontally to the right of the central fixation point at timepoint A (300ms) and remained present until the end of the trial. The healthy control and tAD patients make a single saccade towards the target. The PCA patient takes a long time to initiate their first saccade (in the incorrect direction), followed by a number of small saccades to reach the target location. (B) Example traces from the pursuit task. The figure shows a cycle towards the middle of the trial (seconds 4–8 from a trial of 10 s). Positive values of gaze position indicate rightward gaze. The upper plot (grey line) for each participant shows gaze position in the y (vertical) axis, the lower plot (black line) shows gaze position in the x (horizontal) axis. Target position is represented by a faint blue line. Gridlines show displacement of 1° of visual angle.

Single point localization

In an examination of basic visual functions in 21 patients (mean MMSE 22/30) with PCA, Lehmann et al. (2011) identified single point localization deficits

(evaluated by means of pointing to a single dot displayed for a limited duration) in 60% of individuals. With regard to other basic visual processes, point localization performance only correlated with detection of motion coherence (and not with measures of basic form or colour processing). Similarly with regard to higher order visual skills, point localization performance correlated significantly only with space perception such as VOSP dot counting and number location (and not object perception measures such as fragmented image or silhouette identification), suggesting this up-stream basic deficit in calculating the 3D location of single points in space may partially underpin down-stream difficulties in processing more complex spatial relationships.

In a further study of visuomotor function, PCA patients demonstrated many of the deficits previously reported in individuals with optic ataxia, including 'magnetic misreaching' (a pathological reaching bias toward the point of visual fixation when grasping peripheral targets; Meek et al., 2013). However, in contrast to many reported cases of optic ataxia resulting from non-degenerative disease, PCA patients showed additional deficits (e.g. in grip scaling during memory guided grasping, face and object identification), consistent with the widespread posterior cortical tissue loss common in PCA.

Point localization deficits should also be borne in mind when evaluating visual fields using standard perimetry techniques; though detection rates may vary between quadrants (reflecting variations in the extent of atrophy/dysfunction across the visual cortices), high rates of inconsistency of response to visual stimulation particularly in the periphery suggest the influence of spatial and

attentional factors in contrast to classical dense hemi or quadrantinopias (e.g. Pelak et al., 2011). Point localization deficits are also not restricted to the visual modality; PCA and tAD patients show impairments in stationary sound position discrimination (Golden et al., 2015).

Visual crowding

Crowding is a breakdown in the ability to identify objects in clutter, and particularly impairs object perception in peripheral, amblyopic and possibly developing vision (see Pelli et al., 2004). Excessive crowding has recently been shown to particularly limit object perception in the central vision of PCA patients (Yong et al., 2014). Using centrally-presented tests of letter identification under different flanking and spacing conditions (see Figure 3a), PCA patients were less accurate and slower to identify targets in the condensed than spaced condition even when the target letters were surrounded by flankers of a different category (see Figure 3b). The magnitude of the spacing effect was significantly associated with lower grey matter volume in the right collateral sulcus (see Figure 3c), a region approximating V4 and consistent with fMRI localization data related to peripheral crowding in healthy individuals (Anderson et al., 2012). The spacing effect was also observed for same, but not reverse, polarity flankers; this reverse polarity effect is characteristic of crowding and may reflect low-level segregation of visual information via on and off pathways (Kooi et al., 1994; but see

Chakravarthi and Cavanagh, 2007). The error responses of PCA patients were closely related to averaged target and flanker stimuli (but not individual target or flanker stimuli); this is more consistent with averaging (Parkes et al., 2001; Pelli et al., 2004; Greenwood et al., 2009) than substitution (Wolford, 1975) accounts of crowding. These data indicate that PCA patients experience excessive crowding, reflecting a pre-attentive process that uses averaging to regularize the pathologically noisy representation of stimulus features presented in central vision. Further evidence that excessive crowding is a critical factor underpinning reading problems in PCA comes from studies (both cross-sectional and longitudinal) of two patients who exhibited preserved reading (despite basic visual, visuoperceptual and visuospatial deficits) until the point at which they also developed excessive crowding (Yong et al., 2013, submitted).

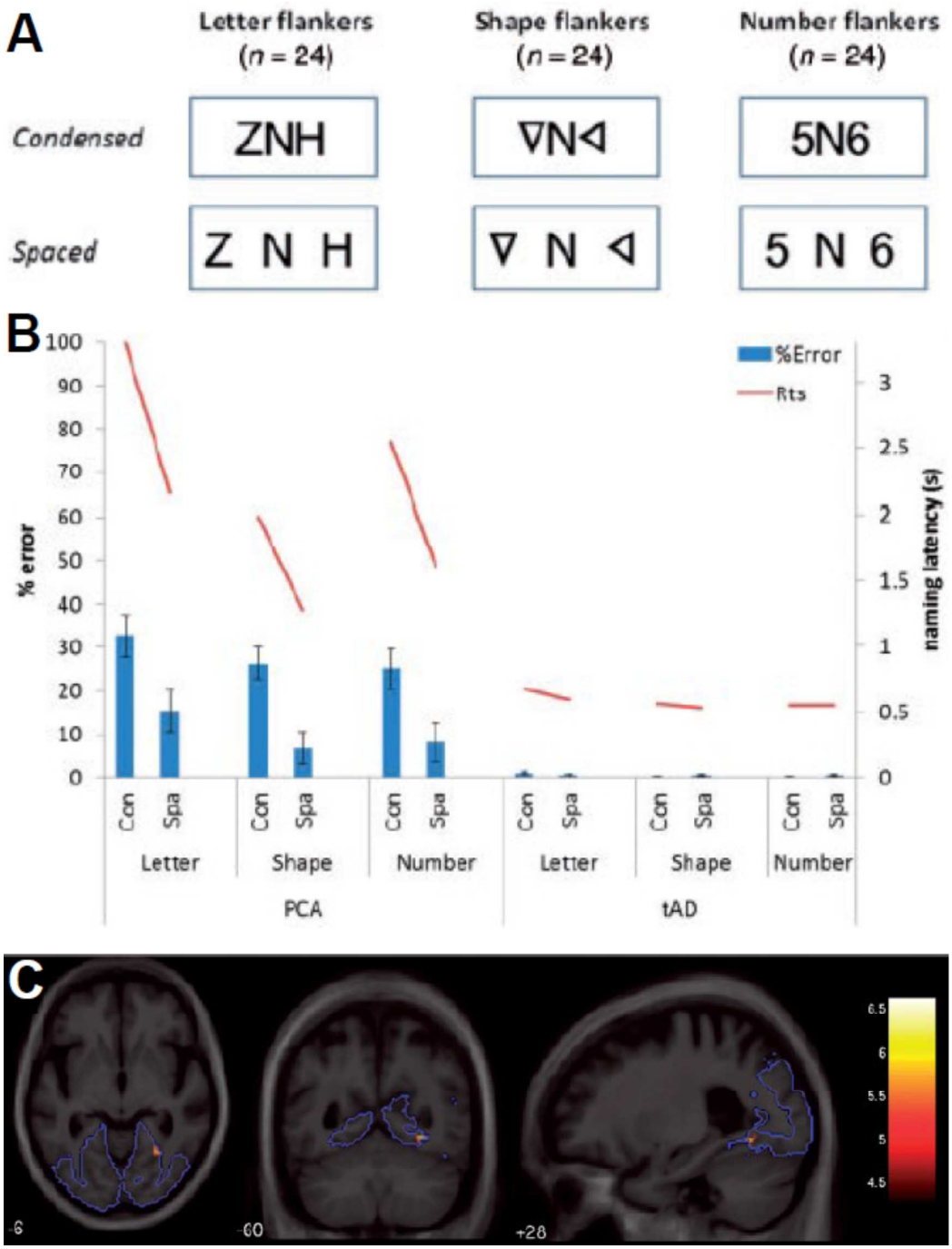

Figure 3. [Prominent effects and neural correlates of visual crowding in](#) *PCA (Yong et al., 2014). (A) Target/flanker arrays used in the letter, shape and number flanker tasks under different spacing conditions. (B) Accuracy and naming latency data for the PCA and tAD group for letter, shape and number flankers in both*

spatial conditions (RT=reaction time, Con=condensed, Spa=spaced). Error bars show standard error. (C) Statistical parametric map (SPM) of grey matter volume associated with a measure of crowding (spacing [shapes/numbers]). The SPM is displayed on axial, coronal and sagittal sections of the custom template in MNI space. When restricting analysis to a pre-specified region of interest (outlined in blue), there was an association between a greater degree of crowding and lower grey matter volume in the collateral sulcus (FWE corrected: p<.05; peak t=6.61, location: x=30 y=-58 z=-8): the colour-map indicates t-values for this association.

Reduced effective field of vision

A common yet striking complaint amongst PCA patients is a difficulty in reading newspaper headlines and other large font sizes whilst continuing to be able to read the small print. This apparent reverse size effect has been reported in a number of individuals with progressive visual imparment (e.g. Coslett et al., 1995; Saffran et al., 1990; Stark et al., 1997), and increased font size has been demonstrated to reduce reading accuracy or speed in 46% of PCA patients (compared to *increasing* reading speed in 18% of tAD patients and 7% of healthy controls; Yong et al., 2014). These effects have been attributed to a reduction in the effective visual field (Crutch et al., 2011; Russell et al., 2004). The influence of stimulus size on single object perception is also reflected in multi-object and complex scene perception, with many PCA patients exhibiting difficulty perceiving the visual world as a coherent whole (Shakespeare et al., 2015b). For example, one PCA patient's description of a picture of Brighton pier and beach

resembled the piecing together of a puzzle: 'It looks like a park or maybe a station or a building site, it looks a bit like the thing they're trying to erect for the Olympics…or it could be the beach because down here looks a bit sandy; yes it looks a bit like Brighton or somewhere like that' (see Crutch, 2014, Figure 3). This impairment in multi-object and complex scene perception (meeting some definitions of simultanagnosia) has been argued to reflect a combination of attentional and spatial working memory deficits (Pisella et al., 2013). Rehabilitative or compensatory strategies are still required, but one elegant study has shown that global processing in such individuals can be enabled by psychophysical biasing of visual pathways (Thomas et al., 2012).

Translation and application

One natural progression from the improving characterization of basic visual function in PCA is to couple this knowledge with a detailed cognitive analysis of everyday activities in order to develop aids and strategies that support individuals with PCA in important everyday functional abilities. One example is an aid currently in development to facilitate reading in PCA (Yong et al., 2015a). Text reading is an early casualty for most people with PCA, with patients missing words, struggling to locate the beginning of the next line, and perceiving motion amongst static words and letters (see Figure 4a and 4b). The aid aims to create the optimal conditions for text reading in PCA by applying perceptual manipulations that minimise or evade many of the oculomotor, basic visual and visuospatial deficits outlined above (fixation instability, visual disorientation, excessive crowding, spatial agnosia and attentional deficits, reduced effective

field of vision). Words are serially presented in a single, central location in order to reduce the challenge of localising words within sentences or identifying the onset of subsequent lines of text (the aid moves the words to where the eyes are, rather than the eyes having to move to where the words are; see Figure 4c). Marking this location with a fixation box serves as a permanent cue to location and hence aid fixation stability. Following reports of PCA patients being able to better localize moving than static stimuli (Crutch, 2014; Midorikawa et al., 2008), the aid successively moves words to fixation as a motion cue to assist disorientated readers. The presentation of individual words was also designed to prevent crowding effects from adjacent words. Furthermore, any risk of the horizontal and vertical line features of the fixation box themselves crowding the target text was attenuated by using opposite contrast polarity (Kooi et al., 1994; Chakravarthi and Cavanagh, 2007). Early data suggest considerable gains in reading accuracy for PCA patients (PCA mean reading accuracy: single-word reading aid = 96%; individual patient improvement range: 6%-270%) relative to standard paragraph reading (PCA 57%; tAD 96%), accompanied by increases in self-rated measures of reading ease, pleasantness and understandability.

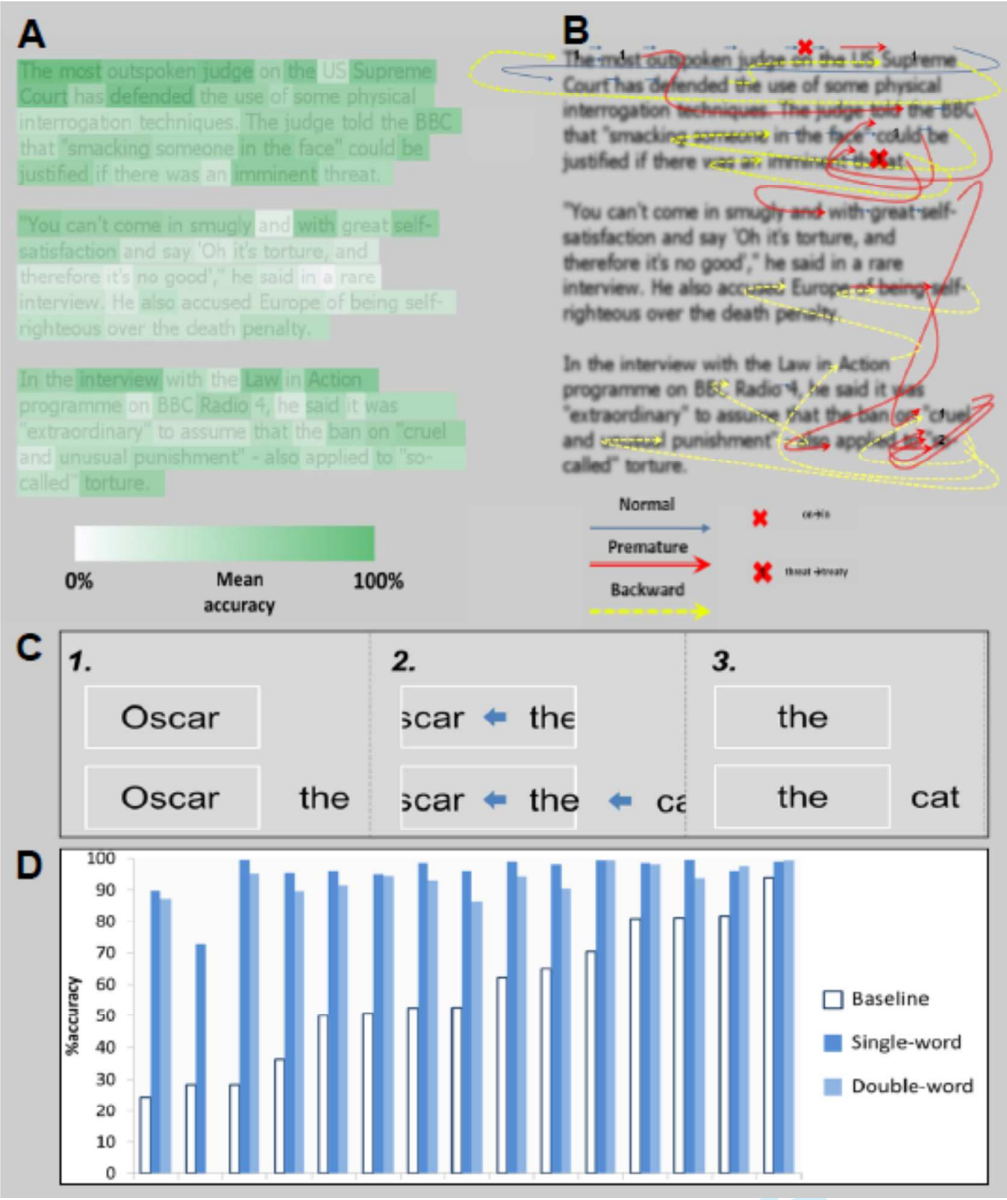

Figure 4. (A) Heatmap of PCA accuracy data from a sample passage (mean group accuracy rates: PCA=57%, tAD=98%, controls=100%). Lighter colours indicate the location of words most commonly missed or misread by PCA patients, and indicate spatial biases towards worse reading in later paragraphs and lines and in the centre of dense, crowded passages of text. (B) Word order from a sample passage for a PCA patient (MMSE score = 22/30). Arrows outline reading order; red arrows

indicate omission of subsequent words through reading later sections of text, and yellow arrows indicate reading of earlier sections of text. (C) Single- and double-word presentations; words appear in the fixation box (1); following participants' responses, successive words move rapidly (2) into the fixation box (3). (D) Individual PCA patients' reading accuracy (percentage correct) for baseline (standard paragraph) and both reading aids (single word and double word), ordered in terms of severity of baseline impairment.

Beyond the dramatic visual deficits seen in PCA, perceptual impairments in people with typical AD and other dementias are greatly under-recognized, and little research has examined the benefits to patient and carer quality of life and mental and physical health that may be achievable by compensating for the effects of cortical visual impairment. This is despite evidence that even simple adaptations to the environment (e.g. using red rather than white tableware to increase visual contrast between food and plate) can have a significant impact on aspects of well-being (e.g. improved eating and drinking in advanced AD; Dunne et al., 2004; see also http://dementia.stir.ac.uk/design/virtual-environments). Several current research projects are focused upon the quantitative evaluation of optometric and cortical visual function in order to improve visual health services for people with dementia (e.g. Hancock et al., 2015) or developing aids to facilitate locomotion and object localization within the home (e.g. Yong et al., 2015b).

Future exploration

PCA is arguably the canonical 'visual dementia'. Nonetheless there remain a number of aspects of vision and visual experience in PCA that remain poorly understood. One outstanding issue relates to the status of visual fields in PCA. Some studies have claimed visual field defects in PCA (e.g. Pelak et al., 2011; Shea et al., 2014; Wan et al., 2015), but computerized visual field perimetry (Humphrey) has revealed poor false negative reliability indices (when a patient fails to see a significantly brighter stimulus at a location than was previously seen) making it difficult to determine to what extent performance reflects attentional deficits and/or true field defects (false negative rate [N=28 evaluations]: mean [SD] 22.3% [19.4%], range 0-66%; Pelak et al., 2011). Another issue is the impact of the cortical degeneration seen in PCA upon the retina and ophthalmic tracts. Preliminary serial diffusion tensor imaging evidence has indicated reductions in the integrity of the posterior thalamic radiations in PCA (Keihaninejad et al., 2012), and investigations of the possible impact of PCA upon the retina are underway (Lengyel et al., 2015). Further work is also required to investigate whether PCA may lead to functional deafferentation of and/or disease propagation along the optic tracts and more anterior parts of the visual system.

Despite these areas of limited understanding, evidence gathered to date and described above regarding basic visual functions (i.e. crowding, point localization, saccade generation, fixation stability) give rise to several future directions for pure and applied psychological research. For example, having

established PCA as a plausible neurodegenerative model of crowding of form information, it remains to be seen whether other forms of visual information (e.g. orientation, colour) exhibit crowding in PCA central vision comparable to that of normal peripheral vision (Wilkinson et al., 1997; van den Berg et al., 2007; Greenwood et al., 2012). Clinically, such information on basic visual dysfunction in PCA will also influence both the design of appropriate visual assessments (see Pelli et al., 2016) and a broader, more informed approach to the evaluation and management of dementia-related visual impairment (College of Optometrists, 2016).

Although deteriorating vision is the presenting complaint for the majority of individuals, it is critical that PCA is not pigeon-holed as solely a visual disorder, and that multisensory and non-visual symptoms and experiences are also investigated and addressed. Three brief examples are illustrative. First, the interactions between vision and other sensory systems have been scarcely examined in PCA despite the key role of the parietal lobes in integrating, ordering and spatially representing information from multiple different senses. Clinical descriptions such as patients asking “Am I the right way up?” (suggesting an inability to relate body position to the gravitational vertical), or reporting an even more extreme complete 180˚ room tilt illusion (reversal of vision metamorphopsia) which could not be explained by impairment of the primary vestibular senses (Crutch et al., 2011), suggest understanding of visuo-vestibular interactions and therapeutic approaches to balance problems in PCA as key areas for future study.

Second, approximately 30% of PCA patients exhibit asymmetrical left upper limb rigidity in addition to their visual dysfunction (Ryan, Shakespeare et al., 2014). These motor deficits are associated with greater asymmetry of atrophy relative to 'pure' PCA patients, particularly involving right frontoparietal and peri-rolandic cortices, putamen, and thalamus. Despite evidence that such individuals are still likely to have underlying Alzheimer's disease, such heterogeneity within PCA offers insights into factors driving phenotypic variation in AD more generally and motivates clarification of the relationship between PCA and other related syndromes such as corticobasal syndrome (CBS).

Finally, individuals with PCA may shed light on processes underpinning the representation of quantity-related verbal concepts. Acalculia is a well-recognised early symptom of PCA, and patients perform poorly on tests of cognitive estimation (Bisbing et al., 2015; Lehmann et al., 2011). However PCA patients also seem to exhibit greater difficulty than typical AD patients processing the precise meaning of non-numerical measurement unit terms (e.g. kilogram, centimetre; Suarez Gonzalez et al., personal communication). These preliminary findings suggest that parietal magnitude and number representations influence or shape anterior temporal lobe-dependent semantic representations of measurement unit terms. Such influence may be analogous to the idea that semantic representations of geographical place names (e.g. America, Cornwall) are spatially coded, that is fundamentally linked to ego- and allocentric representations of the actual geographical location and other spatial concepts (e.g. 'west'; Crutch and Warrington, 2003, 2010).

Summary

Posterior cortical atrophy (PCA) is a focal degenerative condition that dramatically compromises the ability to see what and where things are whilst leaving episodic memory and insight relatively preserved in the early stages. PCA, particularly when attributable to Alzheimer's disease, has attracted much attention from clinical scientists for the questions it raises (e.g. how one disease can affect different individuals in such different ways) and the potential insights offered into fundamental disease mechanisms. Careful observation, systematic neuropsychological investigation and the opportunity to hear the experiences of those living with and caring for someone with PCA have already shed light on a range of classic and less well-studied neuropsychological deficits, and established PCA as a viable neurodegenerative disease model of certain visual phenomena. However, translating this emerging knowledge into compensatory and management strategies and aids which can effect meaningful change in the lives of those affected by dementia-related visual impairment remains a field in its relative infancy.

Acknowledgements

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ordinating Centre (Grant no. ARUK-SRF2013-8). This work was supported by the NIHR Queen Square Dementia Biomedical Research Unit. The Dementia Research Centre is supported by Alzheimer's Research UK, Brain Research Trust (Grant no. EQW 121 301), and The Wolfson Foundation. This work was supported by an Alzheimer's Research UK Senior Research Fellowship and ESRC/NIHR (ES/K006711/1) and EPSRC (EP/M006093/1) grants to SC; The Dunhill Medical Trust [grant number R337/0214] to SC and KY. TS is supported by an Alzheimer's Research UK Research Fellowship.

Recommended readings

Benson, D. F., Davis, R. J., & Snyder, B. D. (1988). Posterior cortical atrophy. *Archives of Neurology, 45*, 789-793.

- The original case series which described and established the clinical concept of PCA.

Crutch, S. J., Lehmann, M., Schott, J. M., Rabinovici, G. D., Rossor, M. N., Fox, N. C. (2012). Posterior cortical atrophy. *Lancet Neurology, 11,* 170–8.

- A thorough review of the clinical, neuroimaging, genetic and pathological literature of PCA, which also emphasizes the need for consensus criteria for clinical diagnosis and research.

Thomas, C., Kveraga, K., Huberle, E., Karnath, H. O., & Bar, M. (2012). Enabling global processing in simultanagnosia by psychophysical biasing of visual pathways. *Brain, 135*, 1578-85.

- An intriguing manipulation of a well-established cognitive effect.

Suárez-González, A., Henley, S. M., Walton, J., & Crutch, S. J. (2015). Posterior cortical atrophy: an atypical variant of Alzheimer disease. Psychiatric Clinics of North America, 38, 211-220.

- A recent review of the neuropsychiatric and psychological features of PCA and appropriate models of patient and carer support.

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